## REMARKS

Claims 1-14 were pending. Claims 2 and 9 have been cancelled without prejudice to pursuing these claims in this or other continuing applications. Claims 1, 3, 5, 8, 10, and 12 have been amended. Upon entry of the present amendments, Claims 1, 3-8, and 10-14 will be pending in this application and under active examination.

The claims have been amended to more particularly and distinctly claim that which the Applicant regards as the invention. In particular, Claims 1 and 8 have been amended to recite that the agent comprises an intracellular calcium chelator that activates surfactant secretion without increasing the cytosolic free calcium concentration ($[Ca^{+2}]i$). Support for this amendment can be found in the specification, *inter alia*, on page 25, lines 1-7.

Amendments to Claims 3, 5, 10 and 12 are formal in nature. Specifically, Claims 3 and 10 are amended to correct the antecedent basis of these claims. Claims 5 and 12 are amended to correct a typographical error therein.

The amendments to the claims do not constitute new matter as defined under 35 U.S.C. § 132. Applicant respectfully requests entry of the amendments.

### I. REJECTION OF CLAIMS UNDER 35 U. S. C. § 103(a)

#### A. Claims Rejected In View of Chander *et al.*

On page 2, Paper No. 3, the Examiner rejects Claims 1, 5-8, and 12-14 under 35 U. S. C. § 103(a) as allegedly being unpatentable over Chander *et al.* (1990) (hereinafter,"Chander *et al.*"). Specifically, the Examiner contends that Chander *et al.* teaches that positive modulators of surfactant secretion in type II cells include calcium ionophores which, in the presence of external calcium and verapamil and in concentrations inhibiting calcium uptake, increased surfactant secretion.

While the Examiner acknowledges that Chander *et al.* does not disclose methods of treating or inhibiting respiratory distress of the claimed invention, it is the Examiner's position that such methods would be allegedly obvious to one of ordinary skill in the art because Chander *et al.* suggests that certain compounds that affect the concentration of calcium in type II pneumocytes are known to increase the secretion of pulmonary surfactant and that pulmonary surfactant deficiency is characterized by respiratory distress. The Examiner believes it would have been within the skill of one of ordinary skill in the art to administer agents disclosed in Chander *et al.* to increase pulmonary surfactant secretion and hence to treat or inhibit respiratory distress. Applicant respectfully traverses the Examiner's rejection for the following reasons.

Applicant respectfully submits that Chander *et al.* does not teach or suggest the invention as claimed. In order to make a *prima facie* case of obviousness, the Examiner must show that alleged prior art teaches or suggests all of the limitations of the claims alleged to be obvious. *In re Royka,* 490 F.2d 981 (CCPA 1974)(holding that to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art). Chander *et al.* does not teach or suggest all of the elements of the rejected claims.

Claim 1 is directed to a method of treating a respiratory distress syndrome in a mammal, comprising administering a therapeutically effective amount of an agent comprising an intracellular calcium chelator that activates secretion of a surfactant from pneumocytes in the mammal without affecting the cytosolic calcium concentration.

There is no suggestion or teaching in Chander *et al.* for the use of an intracellular calcium chelator that activates secretion of surfactants *without affecting the cytosolic calcium concentration.* To the contrary, Chander *et al.* suggests that an increase in the secrection of surfactants, such as PC, is accompanied by an increase in the cytosolic calcium.

In particular, Chander *et al.* states:

> Calcium inophores in the presence, but not absence, of external calcium increased cytosolic calcium in isolated type II cells (96, 112) and PC secretion from rabbit fetal lung slices (78) or isolated type II cells (34, 112). A role for cytosolic calcium is also suggested by the observation that stimulation of cells with ATP increased cytosolic calcium and PC secretion in type II cells (105). These observations suggest that an **increase in cytosolic calcium**

> from external (ionophore mediated) or internal ($IP^3$-mediated release, see *Purinoceptors*) stores is associated with increased PC secretion.

Chader *et al.* (1990), Regulation of Lung Surfactant Secretion, L246, last paragraph. (Emphasis added).

Chander *et al.* does not teach or suggest the claimed method for treating a respiratory syndrome that causes activation of surfactant secretion without an increase in the cytosolic calcium. In fact, Chander *et al.* teaches away from the claimed invention by teaching that an increase in surfactant secretion is accompanied by an increase in cytosolic calcium. Thus, Chander *et al.* does not render the subject matter of Claims 1, 5-8, and 12-14 obvious.

In view of the above, Applicant submits that Claims 1, 5-8, and 12-14 are not *prima facie* obvious under 35 U.S.C. § 103 over the cited reference. Withdrawal of the rejection is respectfully requested.

## B. CLAIMS REJECTED IN VIEW OF STRAYER *ET AL.*

On page 3, Paper No. 3, the Examiner rejects Claims 1-14 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Strayer *et al.* (1990). Specifically, the Examiner contends that Strayer *et al.* teaches that BAPTA-AM, a calcium channel chelators, stimulates surfactant secretion in type II pneumocytes and BAPTA-AM at concentration greater than 10 μM, up to about 100 μM and this stimulation resulted in an increase in surfactant secretions without significantly effecting the viability of the pneumocytes.

While the Examiner acknowledges that Strayer *et al.* does not disclose methods of treating or inhibiting respiratory distress of the claimed invention, it is the Examiner's position that such methods would be allegedly obvious to one of ordinary skill in the art because the prior art amply suggests that certain compounds which effect the concentration of calcium in type II pneumocytes are known to increase the secretion of pulmonary surfactant and that pulmonary surfactant deficiency is characterized by respiratory distress. The Examiner believes it would have been within the skill of one of ordinary skill in the art to administer agents disclosed in

Strayer *et al.* to increase pulmonary surfactant secretion and hence to treat or inhibit respiratory distress. Applicant respectfully traverses the Examiner's rejection for the following reasons.

As a preliminary matter, Applicant submits that Strayer *et al.* is not competent prior art against any claims of this application. The subject matter disclosed in Strayer *et al.* is derived from the Applicant. Strayer *et al.* has published on November 8, 1999.[1] The present application claims priority to a provisional application filed on November 8, 2000, which filing date is not more than one year from the publication date of Strayer *et al.*

Applicant respectfully directs the Examiner's attention to the Declaration of David S. Strayer, M.D., Ph.D. Under 37 C.F.R. § 1.132 ("the Strayer Declaration") submitted concurrently herewith as Exhibit A, which effectively removes the Strayer *et al.* reference as prior art pursuant to M.P.E.P. § 716.10. *In re Katz*, 687 F.2d 450, 455, 215 USPQ 14, 18 (CCPA 1982). The Strayer Declaration clarifies any ambiguity created by the reference regarding inventorship by providing a satisfactory showing that would lead to a reasonable conclusion that Applicant is the sole inventor of the subject matter disclosed in the article and claimed in this application.

Accordingly, Strayer *et al.* is not a Section 102(e)/103 prior art against the present invention. Reconsideration and withdrawal of this rejection is respectfully requested.

## CONCLUSION

In light of the above, Applicants respectfully submit that all pending claims are allowable over the art of record, and a Notice of Allowance is courteously solicited. The foregoing is submitted as a full and complete response to the Office Action mailed March 26, 2003 (Paper No. 3).

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[1] According to an E-mail communication received from the publisher of Strayer *et al.*, this paper was published on line for the first time on November 8, 1999.

The Examiner is invited and encouraged to contact the undersigned attorney of record if such contact will facilitate an efficient examination and allowance of the application.

Respectfully submitted,

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BY _____

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